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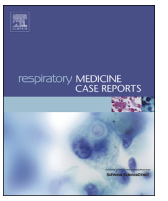

Case Report

Pulmonary manifestation of inflammatory bowel disease: Two case reports

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ABSTRACT

Pulmonary involvement associated with inflammatory bowel disease (IBD) are a rare extraintestinal manifestation (EIM) of inflammatory bowel disease (IBD), we herein presented two cases. Case 1: 53-year-old man with Crohn's disease treated with mesalazine and azathioprine. Pulmonary nodular shadows were incidentally detected on chest imaging, and revealed granulomas through transbronchial lung biopsy. Case 2: 68-year-old man with ulcerative colitis treated with mesalazine. He presented with fever and respiratory symptoms, and chest imaging showed multiple nodular infiltrates. He was diagnosed with organizing pneumonia by lung biopsy. Both cases were diagnosed to have pulmonary involvement associated with inflammatory bowel disease (IBD) according to multidisciplinary examination including positron emission tomography-computed tomography (FDG-PET) and pathological test. Pulmonary manifestations with IBD may not always require discontinuation of drugs or additional use of steroids or immunosuppressants.

1. Introduction

Inflammatory bowel disease (IBD) can have extraintestinal manifestations. Since 1976, a variety of lung manifestations of IBD have been reported [1]. As these manifestations are often subclinical and do not relate to bowel disease activity, they may be more common than previously thought [2]. Moreover, pulmonary involvement may not be recognized by physicians. For the provision of appropriate treatment, differential diagnosis should always be considered, particularly in terms of infections and drug-induced lung pathology. Although pulmonary manifestations in patients with IBD are described in the literature, their evaluation and treatment warrant further investigation. In this article, we presented two cases of IBD that were in remission and complicated by pulmonary manifestations.

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2. Case report

2.1. Case 1

A 53-year-old man was diagnosed with Crohn's disease (CD) 2 years ago after examination with small bowel endoscopy, which revealed longitudinal ulceration and stenosis. He was treated with mesalazine and azathioprine for 3 years and was in clinical remission. Routine computed tomography (CT) showed a 7-mm nodule shadow in the upper lobe of the right lung and a 20-mm nodule shadow with irregularly shaped edges in the lower lobe of the right lung (Fig. 1A, 1B). Positron emission tomography-computed tomography (PET-CT) revealed a very high standardized uptake matching with a right lower lobe nodule shadow (Fig. 1C). Moreover, PET-CT demonstrated physiological standardized uptake values for the nodule shadow in the right upper lobe of the lung. A CT scan performed at 3 months before admission showed only old inflammatory changes in the right upper lobe of the lung. This patient did not develop fever and did not complain of respiratory or gastrointestinal symptoms. Bronchoscopy did not show macroscopic abnormalities. Histopathologic examination through transbronchial lung biopsy (TBLB) of a specimen from the right $B^{8}a$ revealed granulomas combined with chronic inflammatory cells around the bronchus and non-obsolete fibrosis, with absence of malignant cells (Fig. 2). Further analyses with washing cytology, tissue smears, and lung specimen cultures did not lead to the detection of microorganisms. One month after bronchoscopy, both identified lung lesions had decreased in size without discontinuation or modification of the therapeutic agents administered for gastrointestinal CD. Examination performed at 2 months revealed that pulmonary involvement had almost disappeared (Fig. 1D). A repeat CT scan performed after 3 years did not show recurrence of the lesions. Ulcerative colitis (UC) also remained in remission.

PET-CT: positron emission tomography-computed tomography; SUV: standardized uptake value.

2.2. Case 2

A 68-year-old man was diagnosed with left-sided UC 10 years ago in another hospital and was treated with mesalazine and salazosulfapyridine. He was receiving treatment with mesalazine enema for 7 years before the admission due to exacerbation of colitis, and he had been remained in remission. He presented with dry cough and fever (37.6 ˚C) and was admitted to another hospital. There were no neurologic abnormalities or skin lesions. A chest CT scan revealed bilateral pulmonary multiple infiltrate shadows (Fig. 3). Laboratory investigations showed elevated a white blood cell count and C-reactive protein levels. Serologic tests revealed antinuclear antibody levels of $<$40-fold (normal: $<$40-fold), myeloperoxidase-anti-neutrophil cytoplasmic antibody levels of $<$0.5 IU/mL (normal: $<$3.5 IU/mL), serine proteinase3-anti-neutrophil cytoplasmic levels of $<$0.5 IU/mL (normal: $<$2.0 IU/mL), and Krebs von den Lungen-6 levels of 243.3 U/mL (normal: $<$500 U/mL). Although ceftriaxone and azithromycin were administered, the treatment was ineffective. Therefore, he was admitted to our hospital for further investigation and treatment. Bronchoscopy did not reveal macroscopic abnormalities. Bronchoalveolar lavage fluid (BALF) analysis showed a cell count of 5.5×10^{5}/μL, with a cell differentiation of 55.0% neutrophils, 22.0% lymphocytes, 2.0% eosinophils, 21.0% macrophages, and a CD4/CD8 ratio of 2.6. Further analyses of BALF, tissue smears, and lung specimen cultures did not lead to the detection of microorganisms. Histopathological examination of a TBLB specimen obtained from the left B^{1+2} revealed polypoid fibrosis in the alveolar space, which was consisted with organizing pneumonia (Fig. 4). Respiratory symptoms improved rapidly after bronchoscopy, and the patient was followed up without discontin-

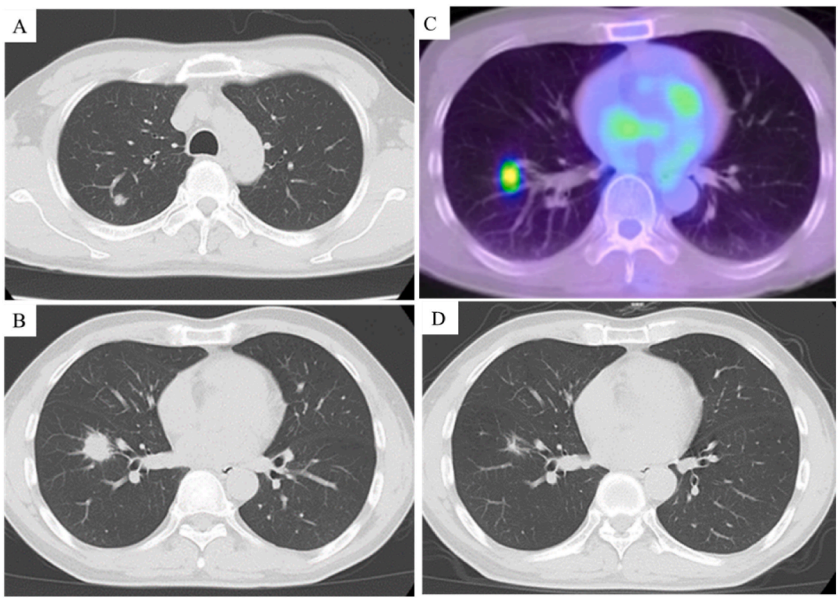

Fig. 1. Computed tomography of the chest showing a 7-mm nodule shadow in the right upper lobe (**A**) and a 20-mm nodule shadow in the right lower lobe (**B**). PET-CT showing SUV-max 4.11 matching with a right lower lobe nodule shadow (**C**). Computed tomography of the chest showing resolution of the nodules at 3 months after admission (**D**).

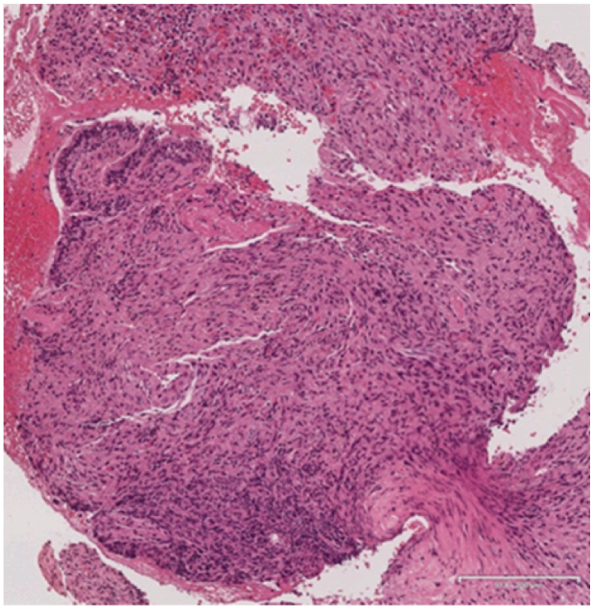

Fig. 2. Pathological findings of Case 1. Histopathological analysis of a biopsy specimen obtained from the right B^8a revealed granulomas with chronic inflammatory cells around the bronchus. Hematoxylin and eosin staining (bar: 100 μm).

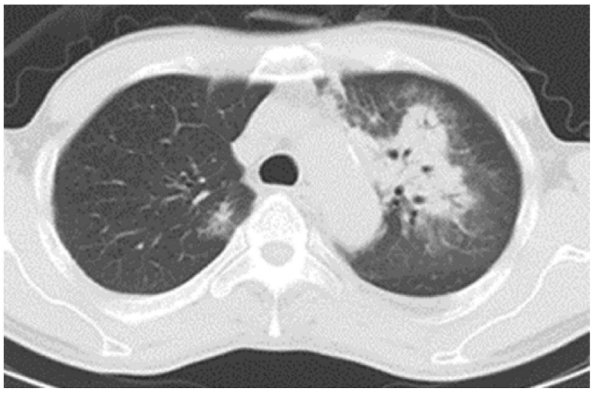

Fig. 3. Computed tomography of the chest showing bilateral pulmonary multiple infiltrate shadows at the time of admission.

uing or altering the medication that have been administered for the treatment of UC. Two months after bronchoscopy, a chest CT scan showed that the indicated infiltrative shadows had almost completely disappeared. Since then, there has been no recurrence of the pulmonary lesions, and gastrointestinal IBD remains in remission.

3. Discussion

IBD is a chronic inflammatory disease that commonly affects the digestive tract, resulting in CD and UC. An estimated 21–41% of patients with IBD will develop extraintestinal lesions during their lifetime [2,3], often involving the skin, joints, and eyes [3]. Lung lesions were first described in 1976 [1]. Since then, various manifestations have been reported, ranging from fatal interstitial lung disease to subclinical lung involvement. Storch et al. described lung involvement associated with IBD as drug-induced disease, anatomic disease, overlap syndromes, autoimmune disease, physiologic consequences of irritable bowel disease, pulmonary function test, and other pulmonary manifestations [4]. Imaging reveals abnormalities in 37–53% of patients [5,6]. However, in a large retrospective study, only 10% of affected patients had respiratory symptoms [6].

Thus far, the pathophysiological mechanisms of pulmonary involvement in IBD have not been elucidated. Nevertheless, both the digestive tract and the bronchial tree are derived from the foregut portion of the endoderm [7,8], and bronchopulmonary disease in IBD may reflect inflammation targeted at different anatomic sites of common embryologic ancestry [9]. Furthermore, patients with IBD exhibit loss of the symbiotic relationship with commensal bacteria in the gut, which affects the microbial composition of mucosal surfaces of other organs (including the lungs). Consequently, neutrophils attack lung epithelial tissue, which is thought to lead to the development of symptoms of pulmonary manifestations in IBD [10].

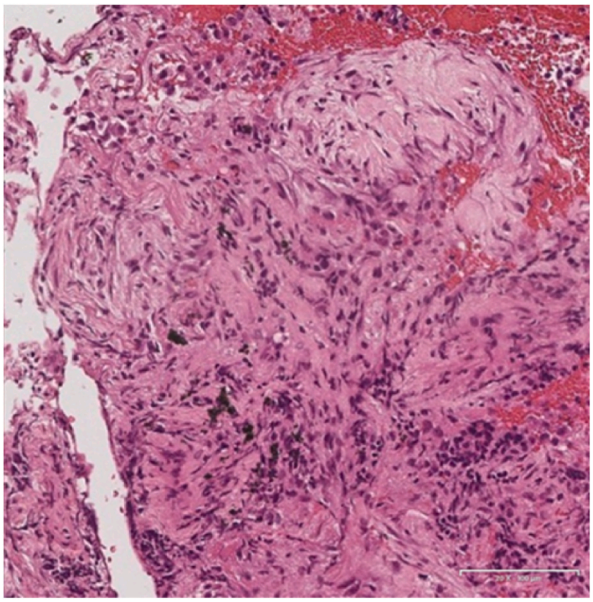

Fig. 4. Pathological findings of Case 2. Histopathological analysis of a biopsy specimen obtained from the left B^{1+2} demonstrated polypoid fibrosis. Hematoxylin and eosin staining (bar: 100 μm).

Parenchymal lung lesions, such as those observed in the two cases discussed in this article, are relatively rare. Approximately half of all parenchymal lung lesions are associated with organizing pneumonia; however, they are rarely linked to eosinophilic pneumonia, non-specific interstitial pneumonia, fibrosis, or necrotic nodules [8]. Chest CT scans may reveal ground-glass opacities, interlobular septal thickening, and irregular linear opacities [11]. If possible, lung biopsy and bronchoalveolar lavage are required for further evaluation.

In the present Case 1, the histopathological analysis showed extensive fibrosis and chronic inflammation with granulomatous changes, which denoted pulmonary manifestations of CD. It is often difficult to distinguish CD from sarcoidosis because both are characterized by granulomatous lesions. In Case 1, the ratio of CD4/CD8 in BALF was 1:2 (i.e., CD8-predominant). Hence, the manifestations of Case 1 were not absolutely indicative of sarcoidosis. Case 2 was pathologically identified as organizing pneumonia, which is the most commonly observed type of parenchymal lung lesion in IBD [12,13]. Other parenchymal lung lesions (e.g., necrotic nodules, interstitial pneumonia, lymphocytic interstitial pneumonia, and eosinophilic pneumonia) have been reported, and the phenotype of these lesions varies [8,14].

Drug-induced diseases, infection caused by immunosuppressive medications, and pulmonary embolism are not proper IBD associated disease [15,16], but there are known as Critical complications caused to the lungs in patients with IBD. It is often difficult to distinguish between parenchymal lung involvement and drug-induced disease in IBD. Sulfasalazine and mesalamine have been used for the long-term treatment as a therapeutic agent for IBD. However, it can lead to interstitial lung disease, and in almost half of the reported cases peripheral eosinophilia was observed [4,17]. In addition, azathioprine is therapeutic options for patients with moderate to severe CD. Pulmonary toxicity due to azathioprine has been associated with drug use has been rarely reported in the literature, although interstitial pneumonitis, restrictive lung disease, Goodpasture-like syndrome and pulmonary hemorrhage have been documented after use of azathioprine. Infectious pneumonia is the most common cause of pulmonary symptoms in IBD patients undergoing immunosuppressive therapy including azathioprine [18].

Currently, there is no established treatment for pulmonary involvement in IBD. Therefore, such patients often receive steroids or immunosuppressive/biologic agents after exclusion of pulmonary infection and discontinue medication administered for the treatment of IBD [19–23]. Although the response to systemic steroid therapy is generally good, the disease can be refractory in some cases and lead to repeated relapses. Although rare, there have been reports of resolution of parenchymal lung manifestations in IBD without alterations or discontinuation of therapeutic agents, as in the present cases [19,24–26] (Table 1).

Table 1 included several CD cases that displayed various symptoms, but none of them received immunosuppressive treatment when pulmonary involvement was discovered. Furthermore, only one case of UC has been reported to date where lung lesions resolved spontaneously. Case 1 presented the first report of CD with pulmonary involvement that resolved spontaneously during treatment with immunosuppressive drugs and 5-aminosalicylate. In contrast, Case 2 is distinct from previously reported cases of UC, as it involved pulmonary lesions with respiratory symptoms that spontaneously resolved. These findings suggested that pulmonary involvement with IBD may resolve spontaneously regardless of medication use or clinical symptoms. Additionally, we thought that the appearance and disappearance of pulmonary involvement could not be related to the course of IBD.

Changes in treatment can have a significant impact on the lives of IBD patients who are in remission. When drug-induced or infectious disease can be ruled out by clinical findings including pathological examination and the disease does not progress rapidly, discontinuation of therapeutic agents or the addition of steroids or immunosuppressive drugs may not be necessary, such as in our cases.

Table 1
Cases of lung parenchymal manifestations in IBD.

Ref. no.	Age/ Sex	Symptoms and/or physical findings	Chest CT findings	Histopathology of the lungs and method of tissue biopsy	Status of UC/CD	Therapy for UC/CD until the onset of pulmonary abnormalities	Outcome
[15]	17 years, female	CD with severe malnutrition, diarrhea, perianal abscess (no respiratory symptoms)	Tree-in-bud opacities predominantly in the bilateral lower lobes of the lung	VATS with necrotizing granuloma and organizing pneumonia	Active	No medication	Resolution of radiographic abnormalities
[15]	14 years, female	CD with chest pain and cough	Bilateral pulmonary nodules with central cavitation	VATS with necrotizing granuloma and organizing pneumonia	Remission	No medication (previously treated with infliximab and prednisone)	Resolution of radiographic abnormalities
[20]	77 years, female	CD without respiratory or intestinal symptoms	Bilateral pulmonary multiple masses	VATS with marked fibrosis and non-caseating granulomas	Remission	No medication	Resolution of radiographic abnormalities
[21]	64 years, male	10-year history of CD with productive cough, dyspnea, and weight loss approximately 5 years after initial diagnosis	Multiple pulmonary nodules	VATS with scattered epithelioid granulomas	Remission	No medication (previously treated with mesalamine and occasional steroid therapy)	Resolution of radiographic abnormalities
[22]	17 years, female	UC without respiratory or intestinal symptoms	Bilateral pulmonary nodules, one of which included a central cavitation	TBLB with macrophages in the alveolar space and neutrophilic infiltrates	Remission	Mesalazine	Resolution of radiographic abnormalities

CD: Crohn's disease; IBD: inflammatory bowel disease; TBLB: transbronchial lung biopsy; UC: ulcerative colitis; VATS: video-assisted thoracic surgery.

4. Conclusion

The possibility of IBD-related pulmonary disease should be considered following the detection of abnormal chest shadows and abnormal respiratory function. It is often difficult to distinguish this type of disease from infectious and drug-related diseases, and use of a lung biopsy can help define a course of treatment for such cases. Although rare, parenchymal lung lesions may resolve spontaneously. Careful judgment is required when considering to discontinue or alter medications administered for the treatment of IBD.

Author contributions

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Investigation: Jun Omori, Yasuhiro Terasaki, Toru Tanaka, Kazue Fujita, Natsuki Takano, Yumi Sakurai, Miyuri Suga, Anna Hayashi, Ken Okamura, Yoshinobu Saito.

Review: Kazuo Kasahara, Katsuhiko Iwakiri, Kaoru Kubota, Masahiro Seike.

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Declaration of competing interest

None.

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